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Full Length Article

Difficulties in psychosocial functioning due to current depressive symptoms: What can C-Reactive protein tell us?

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ABSTRACT

Background: Multiple empirical studies and meta-analyses have examined how inflammation may be associated with various aspects of major depression, with older adults being particularly at risk for the effects of inflammation-related depression. Despite this wide area of research, no study has examined how depression-related inflammation impacts psychosocial functioning.

Methods: Data from the National Health and Nutrition Examination Survey, years 2007–2008, were utilized to examine whether adults over the age of 40 experienced difficulty in their work, taking care of things at home, or getting along with other people due to current depressive symptoms through a logistic regression analysis. We selected C-reactive protein (CRP), a common marker of immune system activation, as our primary predictor of interest while controlling for relevant covariates.

Results: Greater CRP was positively associated with a greater risk for individuals experiencing difficulties in psychosocial functioning due to depressive symptoms. While current number and severity of depressive symptoms was also found to be significant in the model, comparison of effect sizes identified that CRP appears to be a more relevant marker for experiencing difficulty than a number of relevant biopsychosocial covariates.

Conclusion: Inflammation as measured by CRP may be a helpful tool in understanding how depressive symptoms are associated with an individual's ability to successfully navigate their social environment. Results here demonstrate the emerging utility of CRP in helping to assess the risk for negative outcomes in those experiencing depressive symptoms, especially as it pertains to older adults.

1. Introduction

Major Depression (MD) is one of the most common forms of mental illness, affecting roughly one in five individuals in the U.S. over the life course (Hasin et al., 2018). Typically, MD is characterized by at least a two-week period of decreased mood or anhedonia and is often accompanied by a combination of vegetative disturbance, cognitive difficulties, and, at times, suicidal ideations (American Psychiatric Association, 2013). Episodes of MD are often accompanied by complicating factors such as a high degree of anxious distress and medical comorbidities (Hasin et al., 2018; Rugulies, 2002), and for many, these episodes may leave them unable to function in the same capacity as prior to onset of depression, leading to as many as 400 million disability days, annually (Merikangas et al., 2007). Thus, studies are needed to understand the onset and pathogenesis of MD so that it can be prevented, mitigated, and treated.

The growth of psychoneuroimmunology over the past twenty years has provided numerous insights into MD, with many studies focusing on the association between MD and C-reactive protein (CRP), an acute phase protein produced in the liver that is associated with the activation of the body's inflammation system (Pariante, 2017). While effect sizes vary across studies, the association has been noted in several recent meta-analyses, (Osimo et al., 2019, 2020; Smith et al., 2018; Horn et al., 2018), and CRP has been found to be indicative of other common inflammatory markers that are frequently tied to MD (Felger et al., 2020). Additionally, the large number of empirical studies have covered a range of aspects of MD, including degree of depressive symptoms (Kohler-Forsberg et al., 2017), risk for antidepressant treatment resistance (Haroon et al., 2018), persistence of depressive symptoms (Zalli et al., 2016), increased risk for hospitalization (Wium-Andersen et al., 2013), and increased risk for specific depressive symptoms (Kohler-Forsberg et al., 2017; Felger et al., 2016; Duivis et al., 2013). This association is particularly concerning for older adults, as recent meta-analytic findings have identified that increased activation of the inflammation system, as

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measured by both CRP and other immune markers, is associated with cross-sectional and longitudinal risk for depression in adults ages 50 and over (Smith et al., 2018). This meta-analysis included 17 studies that evaluated unidirectional and bidirectional associations between CRP and depression in community dwelling older adults, identifying that inflammation as measured by CRP most likely leads to future depressive symptoms. Reinforcing these results and the risk to older adults, an additional study found that increased levels of CRP are associated with late-onset depression (after age 60) rather than early onset (before age 60) (Rozing et al., 2019).

Despite this wealth of findings, studies have been inconsistent in their methods, leading to concerns over the replication and reproducibility of studies that assess the relationship between CRP and various aspects of MD (Horn et al., 2018). Indeed, a host of covariates in the areas of medical health have garnered considerable attention, especially for older adults who tend to have greater rates of chronic illness which are associated increased pro-inflammatory signaling (Taylor et al., 2013; Gold et al., 2020), but who have also been found to demonstrate a stronger association between CRP and MD (Mac Giollabhui et al., 2020). Additionally, CRP may be related to active infection or disease when in the context of emergency or inpatient health settings (Sproston and Ashworth, 2018), and has also been found to be positively associated with an individual's body mass index (BMI) (Ambrosio et al., 2018). Furthermore, some evidence suggests that individuals who currently have MD and a CRP level of 3.0 mg/L or greater are more likely to meet criteria for obesity (Rethorst et al., 2014).

Beyond medical health, significant research has also emerged with respect to various lifestyle factors such as tobacco and alcohol use, sleep behavior, and physical activity. Indeed, moderate alcohol consumption, as defined by 1–7 alcoholic drinks, has been found to be associated decreased CRP levels, and a study of older adults (mean age 74) found that moderate alcohol consumption was associated with both lower amounts of depressive symptoms and CRP levels (Paulson et al., 2017). With respect to tobacco use, tobacco cigarette smoking has been found to be associated with higher levels of CRP in individuals currently experiencing MD (Nunes et al., 2012), and those with MD who also smoke have been found to have a greater degree of disability for work, higher severity of depression, and a greater number of suicide attempts (Vargas et al., 2013). In turning to factors related to sleep, decreased sleep has been a well-documented risk factor for future MD episodes (Wiebe et al., 2012), and CRP levels have also been found to be elevated in a laboratory test of individuals who slept less than 4 h relative to individuals who slept 8 h (O'Connor et al., 2009). Lastly, some evidence suggests that increased physical activity may be effective in reducing MD symptoms (Kvam et al., 2016), and longitudinal studies of physical training programs have found reductions in CRP levels (Plaisnace and Grandjean, 2006).

While the literature around CRP levels and depressive symptoms is broad, little research has been published that examines the connection between CRP and how individuals experiencing depression may have difficulty with psychosocial functioning. To our knowledge, the study completed by Wium-Andersen et al. (2013) has been the only study to examine the relationship between CRP, psychological distress, and MD, concluding that psychological distress among those with a treatment history of depression was related to elevated CRP in the general population. Despite the strengths of their study, psychological distress was measured by binary response to feeling that one had not accomplished much, felt nervous or stressed, and wanted to give up. Thus, psychological distress could not be tied back directly to the experiences of depression. Additionally, while Wium-Andersen and colleagues' (2013) study exercised appropriate control of covariates through the inclusion of variables related to alcohol consumption, smoking status, leisure-time physical activity, income, education, history of chronic disease, and BMI, the inclusion of social support was absent from analyses.

Social support can be most comprehensively defined as the perception that one is loved, cared for, esteemed, or valued by others through membership of a social network of mutual assistance and obligations (Taylor, 2011). One of the most common ways that social support is studied when addressing physical and mental health outcomes is through the lens of the stress buffering hypothesis, which proposes that social support protects individuals from the pathogenic effects of stress (Cohen and Wills, 1985). This model follows a five-step process in which a stressful event happens, the event is appraised, the event is interpreted as stressful, there is a physiological or behavioral response, the response is associated with later illness or illness behavior (Cohen and Wills, 1985; Uchino et al., 2018a). The stress buffering effects of social support in the context of depressive illness is supported by a recent meta-analysis of 47 studies which found that lower inflammatory markers, including CRP, were associated with greater social support (Uchino et al., 2018b).

Given that the literature has demonstrated an association between CRP and various aspects of MD, the present study seeks to build on the prior work examining the basic premise of a possible relationship between CRP and experiencing difficulty due to current depressive symptoms. Through examination of this relationship, along with empirically relevant covariates such as medical health, substance use, and social support, we derived the following questions:

1. Does CRP have a significant relationship with the odds of an individual experiencing difficulty due to their depressive symptoms?
2. Does social support mitigate the odds of an individual experiencing difficulty due to current depressive symptoms?
3. Do empirically relevant covariates continue to function similarly as they do in prior empirical studies when evaluated on the odds of an individual experiencing difficulty due to current depressive symptoms?

2. Method

2.1. Data set and participants

The present study utilizes secondary data from the National Health and Nutrition Examination Survey (NHANES), specifically the data collected during a 12-month period spanning 2007–2008 (NHANES 07–08). The NHANES is conducted annually by the Center for Disease Control (CDC) via a four-stage sampling process designed to construct a nationally representative sample of the population of the United States. This is done by sampling at the county level, segments of that county, blocks of households within the county segments, and finally at the individual level within the household. The survey sampled non-institutionalized individuals from across all 50 states (see Zpif et al., 2013 for an overview of survey methodology). Total responses for the data set included 10,149 respondents; however, only 5447 individuals provided who were age 18 and above provided data for the PHQ-9. Individuals were included for analyses only if they experienced decreased mood and/or anhedonia for "several days" over the last 2 weeks as measured by self-report on the first two questions of the Patient Health Questionnaire-9 (PHQ-9) (n = 1862), and if they provided data for all relevant categorical variables included in this study (n = 1708). Regrettably in the NHANES, measures of social support (number of past year church attendances, number of close friends, perception of no financial support, and perception of no emotional support) were only administered to individuals 40 years of age and older, resulting in an age floor of 40 for the sample (n = 1005).

2.2. Difficulty due to depression

The dependent variable for this study was if the individual experienced difficulty doing their work, taking care of things at home, or getting along with people due to current depressive symptoms within a subsection of the PHQ-9. Responses offered to participants included not at all difficult, somewhat difficult, very difficult, or extremely difficult. From these options, somewhat difficult, very difficult, and extremely difficult responses were collapsed into "experienced difficulty due to

current depressive symptoms," while not at all difficult was collapsed into "did not experience difficulty due to current depressive symptoms." The decision to dichotomize difficulty due to depression was based on the small cell size of the "extremely difficulty" category, as well as to understand categorically if symptoms are interfering with an individual's ability to function in their social environment as is outlined in the DSM-5 (American Psychiatric Association, 2013).

2.3. Depressive symptoms

Total PHQ-9 scores were also included in the present study as a predictor variable. The scale is composed of ten questions, nine of which each correspond to an individual symptom of depression in the Diagnostic and Statistical Manual-IV, while the tenth question is a measure of the degree to which depressive symptoms affect an individual's ability to function (utilized here as the dependent variable). The nine main questions that assess depressive symptoms are scored from 0 to 3 with 0 indicating "not at all," 1 indicating "several days," 2 indicating "more than half the days," and 3 indicating "nearly every day." While scores typically range from 0 to 27, because included participants confirmed decreased mood and/or anhedonia, the PHQ-9 utilized in this study had a score floor of 1. Prior investigation of the psychometric properties of the PHQ-9 have found similar convergent and discriminant validity to the Beck Depression Inventory-II, as well as being sensitive to change over time (Titov et al., 2011; Kroenke et al., 2001; Lowe et al., 2004). Computation of Cronbach's alpha for the present sample yielded an alpha of 0.79 indicating acceptable reliability.

2.4. C-reactive protein

C-reactive protein has been commonly found to be elevated in some, but not all, cases of MDD, and an elevated baseline of CRP has been found to be positively associated with increased psychosocial stress. Blood samples of 1.0 mL, but at least 0.3 mL, were collected from participants by venipuncture at a mobile examination center before being frozen and shipped to the University of Washington for analysis. Latex-enhanced nephelometry was used to quantify CRP levels. The assay has a lower detection limit of 0.02 mg/dL, with any value below the detection limit being reported as the lower detection limit divided by the square root of 2. All participants were asked to fast for 9 h prior to specimen collection, including those individuals diagnosed with diabetes who are taking insulin; however, as an additional check, participants who confirmed to have consumed caffeine ($n = 11$), alcohol ($n = 1$), or cigarettes ($n = 25$) at least 30 min prior to specimen collection were not included. Venipuncture was performed only once participants were seated on an examination table; however, if it was not possible for the participant to sit upright for the procedure they were then placed in the supine position. A full review of laboratory procedures for CRP collection and measurement are publicly available for review (CDC, 2007).

While some studies have excluded individuals with CRP values greater than 10.00 mg/L, some evidence suggests that values above 10.00 mg/L may be associated with greater depressive symptoms (Moriarity et al., 2021). Thus, in conjunction with recommendations by Horn et al. (2018), CRP values of the mean plus three times the standard deviation were winsorized to retain the ordinal nature of CRP values while minimizing the influence of extreme values, resulting in a range of 0.01–4.06 mg/dL (0.01–40.6 mg/L). Winsorization of CRP values only affected the top 1% of values for this measure.

2.5. Covariates

Social Support**.** Four measures were included to survey social support: number of close friends, number of times attended church per year, perception of financial assistance, and perception of emotional support. Both the number of close friends and number of times that a participant attended church were self-reported continuous variables with the analyzed sample ranging from 0 to 50 and 0–365, respectively. Perception of financial support was assessed by asking participants "If you need some extra help financially, could you count on anyone to help you; for example, by paying any bills, housing costs, hospital visits, or providing you with food or clothes." Participant responses were recorded as yes (0) or no (1). Perception of emotional support was measured by asking participants "in the last 12 months could you have used more emotional support than you received?" Responses were categorically reported as yes (1) or no (0).

Biometric measures of health. Several additional variables were included as measurements of health: body mass index (BMI), triglycerides (mg/dL), cholesterol (mg/dL), systolic and diastolic blood pressure, and reported history of a medical condition. Body mass index was treated as continuous and was pre calculated in the NHANES 07–08 data set by dividing participants' weight in kilograms by their height in meters squared. Systolic and diastolic blood pressure were both included as continuous measures. Both triglycerides and cholesterol were derived from participants' serum and were included as continuous measures. Lastly, self-reported history of arthritis, congestive heart failure, coronary heart disease, angina, heart attack, asthma, gout, stroke, emphysema, thyroid problem, chronic bronchitis, liver condition, cancer or malignancy as previously diagnosed by a doctor was categorically coded as either a confirmed history (1) or denied history (0) so as to account for broad history of a medical condition.

Tobacco and alcohol. We included measurement of both alcohol and tobacco cigarette use. Alcohol use was measured via the average number of alcoholic drinks an individual consumed per day, with a range of 0–12 alcoholic drinks. Individuals who consumed 13 or more drinks were removed from analyses as extreme alcohol consumption may affect CRP levels. Tobacco cigarette use was trichotomized into three groups: those with no history of smoking, those who smoked cigarettes in the past and now abstain, and those that currently smoke cigarettes. Those with no history of smoking cigarettes were selected as the reference group.

Prescription medication use. Use of five prescription medication categories were included as covariates for their known influence on MD, CRP, or both. Use of any selective serotonin reuptake inhibitor (SSRI), Aspirin, diuretic, beta blocker, or ACE inhibitor were coded as "reported use (1)" or "denied use (0)" for each respective category. For any medication that included one of the five prescription categories as a part of a medication's formulation it was also coded as reported use (ex: reporting use of Symbyax was coded as reported use for SSRI's).

Physical activity. Two measures of vigorous physical activity were included. Vigorous recreational activity was coded as confirmed (1) or denied (0) based on participant's response to the question "do you do any vigorous-intensity sports, fitness, or recreational activities that cause large increases in breathing or heart rate like running or basketball for at least 10 min continuously?" Vigorous work activity was also coded as confirmed (1) or denied (0) with participants being asked to think of vigorous-intensity activities as "require hard physical effort and cause large increases in breathing or heart rate like carrying or lifting heavy loads, digging, or construction work for at least 10 min continuously."

Sleep. Sleep was assessed via average number of hours slept per night and how often the participant felt they did not get enough sleep. Average number of hours slept per night was included as a continuous measure with responses ranging from 1 to 12 h per night. Notably, any amount of sleep more than 12 h per night were coded as 12 h per night. Participants responded to how often they did not get enough sleep via a five-point Likert scale with possible responses ranging from "never," "rarely (1 time a month)," "sometimes (2–4 times a month)," "often (5–15 times a month)," or "almost always (16–30 times a month)."

*Demographics***.** Race/ethnicity, age, gender, education level, and income to poverty ratio were included as relevant demographic covariates. Respondents self-reported their race/ethnicity as non-Hispanic White, non-Hispanic Black, Mexican American, other Hispanic, or other including mixed racial identity. Age was recorded in years with a possible response range from 1 to 80, with all individuals over the age of 79 being

Table 1
Descriptive statistics.

	N or M (SD)	% or Range	Raw N
Difficulty due to depression	15,077,623	45.87%	964
PHQ 9	6.892 (4.811)	1–27	958
Biological measures			
CRP (mg/dL)	0.472 (0.737)	0.01–4.06	919
BMI	29.247 (6.947)	15.25–63.95	951
Triglycerides (mg/dL)	174.284 (130.530)	24–1460	907
Systolic Blood Pressure	126.664 (19.441)	78–222	922
Diastolic Blood Pressure	72.090 (13.499)	0–110	922
Cholesterol (mg/dL)	205.664 (44.707)	97–390	908
Chronic Condition	22,569,602	68.66%	964
Social Support			
Close friends	6.592, (6.541)	0–50	960
Church attendance	31.718 (49.016)	0–365	964
No financial support	8,464,068	25.75%	964
No emotional support	10,307,980	31.36%	964
Tobacco and Alcohol			
Current cigarette use	7,783,038	23.68%	964
History of cigarette use but current abstainer	16,738,527	50.92%	964
No history of cigarette use	8,351,231	25.36%	964
Number of alcoholic beverages per day	1.337 (1.784)	0–12	964
Sleep			
Average number of hours slept	6.667 (1.539)	1–12	964
How often did you not get enough sleep	1.972 (1.344)	0–4	961
Physical Activity			
Vigorous work activity	5,323,682	16.19%	964
Vigorous recreational activity	3,473,581	10.57%	964
Prescription Medication Use			
SSRI	1,357,246	4.13%	964
Aspirin	272,616	0.83%	964
Diuretic	2,200,347	6.69%	964
Beta blocker	1,931,029	5.87%	964
ACE inhibitor	379,486	1.15%	964
Demographics			
Gender (male)	12,230,862	37.21%	964
Race: Non-Hispanic White	23,785,524	72.36%	964
Race: Non-Hispanic Black	3,855,261	11.73%	964
Race: Mexican American	1,832,536	5.57%	964
Race: Other Hispanic	1,418,357	4.31%	964
Race: Other race/ethnicity	1,981,118	6.03%	964
Age	55.841 (11.840)	40–80	964
Household income to poverty ratio	2.878 (1.625)	0–5	886
Education Status	3.344 (1.213)	1–5	962

PHQ9: Patient Health Questionnaire 9, CRP: C-reactive protein, BMI: body mass index, SSRI: selective serotonin reuptake inhibitor.
Raw N values indicate the number of individuals that provided data for the predictor prior to sample weight application.

coded as age 80. Ratio of family income to poverty was included as a measure of relative socio-economic status. This was calculated by dividing family income by poverty guidelines specific to family size, location, and year, with higher values indicating greater relative affluence. The responses to this variable range from 0 to 5.00, with any score above 4.99 being recorded as 5.00 to protect the identity of respondents. Lastly, current education was included as an ordinal variable with response ranging from "less than 9th grade (1)," "9–11th grade (includes 12th grade with no diploma) (2)," "high school graduate/GED or equivalent (3)," "some college or associates degree (4)," "college graduate or above (5)."

2.6. Data analysis plan

All analyses were performed in SAS University Edition. Prior to any analyses two participants were removed from the data set due to elevated triglyceride levels (2100 mg/dL and 3281 mg/dL, respectively), as well as two other participants per reported consumption of more than 12 alcoholic drinks per day (O'Connor et al., 2010; Horn et al., 2018). Furthermore, included participants were confirmed to not have a head or chest cold, stomach or intestinal illness, flu, pneumonia, or ear infection in the last 30 days prior to their participation in the study. These removal decisions, including those related to CRP collection, included 37 participants, leaving a final analytical sample of 964. The number of respondents that provided data for each variable can be located in Table 1.

In accordance with recommendations from the CDC, data for the analyses were weighted with the variable weight included in the NHANES 07–08 data set per the inclusion of data gathered from the mobile examination centers. This weighting resulted in a sample size of 32,872,796. We utilized a logistic regression to examine the relationship between CRP and difficulty associated with current depressive symptoms in a group of individuals endorsing self-report depressive symptomatology. To strengthen the model, we included several covariates that are supported by the literature as having an effect on MD, CRP, or both (O'Connor et al., 2009; Horn et al., 2018). These covariates include biometric measures of health, social support measures, tobacco and alcohol use, physical activity, relevant prescription medication use, and demographics. Odds ratios were calculated with a 95% confidence interval for all predictor variables. All variables were examined at the univariate and bivariate level before being entered into the multivariate model simultaneously. A Chi Square test was utilized to analyze the relationship between categorical predictors and the dependent variable, while pooled variance t-tests tests were utilized to analyze the relationship between continuous predictors and the dependent variable. A correlation matrix of all continuous predictors was included to help understand the relationships between continuous predictors. Variance inflation factor was calculated for all predictor variables and did not

Table 2
Associations with difficulty due to depression.

	Difficulty	No Difficulty	t or (X^2)
	% or M(SD)	% or M(SD)	
PHQ 9	9.253 (5.258)	4.901 (3.269)	−15.61**
Biological Measures			
CRP (mg/dL)	0.547 (0.861)	0.410 (0.609)	−2.82**
BMI	28.937 (6.840)	29.510 (7.025)	1.27
Triglycerides (mg/dL)	177.661 (134.745)	171.444 (126.806)	−0.71
Systolic Blood Pressure	125.381 (19.624)	127.782 (19.211)	1.87
Diastolic Blood Pressure	72.641 (13.804)	71.609 (13.209)	−1.16
Cholesterol (mg/dL)	205.470 (46.172)	205.823 (43.441)	0.12
Chronic Condition Present	34.81%	33.85%	(677,979)**
Chronic Condition Absent	11.06%	20.29%	
Social Support			
Church attendances	28.458 (45.470)	34.480 (51.670)	1.90
Close friends	5.594 (4.722)	7.439 (7.654)	4.39**
Enough emotional support	27.29%	41.35%	(1,082,175)**
Not enough emotional support	18.58%	12.78%	
Financial support	31.63%	42.62%	(406,199)**
No financial support	14.23%	11.52%	
Demographics			
Age	54.222 (11.362)	57.213 (12.075)	3.93**
Education	3.319 (1.185)	3.364 (1.236)	0.57
Household income to poverty ratio	2.694 (1.660)	3.031 (1.578)	3.09**
Gender: Male	18.10%	19.11%	(60,574)**
Gender: Female	27.77%	35.03%	
Race: non-Hispanic White	34.21%	38.15%	(93,768)**
Race: non-Hispanic Black	4.81%	6.92%	
Race: Mexican American	2.48%	3.09%	
Race: other Hispanic	1.63%	2.68%	
Race: other	2.74%	3.29%	
Tobacco and Alcohol			
Current smoking	12.87%	10.81%	(681,871)**
Smoking History	14.04%	13.20%	
No smoking history	18.96%	30.12%	
Number of alcoholic drinks	1.339 (1.761)	1.334 (1.804)	−0.04
Prescription Medication Use			
SSRI	2.66%	1.47%	(197,239)**
No SSRI	43.20%	52.67%	
Aspirin	0.14%	0.69%	(92,297)**
No Aspirin	45.73%	53.45%	
Diuretic	2.37%	4.32%	(102,944)**
No Diuretic	43.49%	49.81%	
Beta blocker	2.51%	3.36%	(7783)**
No Beta blocker	43.35%	50.77%	
ACE inhibitor	0.41%	0.75%	(16,778)**
No Ace inhibitor	45.46%	53.39%	
Physical Activity			
Vigorous Work Activity	36.33%	47.48%	(435,559)**
No Vigorous Work Activity	9.54%	6.65%	
Vigorous Recreational Activity	40.72%	48.71%	(12,561)**
No Vigorous Recreational Activity	5.15%	5.42%	
Sleep			
Hours Slept per night	6.484 (1.736)	6.821 (1.331)	3.40**
Not enough sleep	2.235 (1.374)	1.749 (1.276)	−5.67**

PHQ9: Patient Health Questionnaire 9, CRP: C-reactive protein, BMI: body mass index, SSRI: selective serotonin reuptake inhibitor.
*p < 0.05, **p < 0.01.

indicate multicollinearity. To assess for the influence of missingness or exclusion, two additional multivariate models were constructed: the first excluding social support variables which allowed for the inclusion of individuals ages 20–40, and the second excluding the family income to poverty ratio variable which was the predictor with the highest degree of missingness (8.1%).

3. Results

Nearly half of the individuals in the study experienced difficulty due to current depressive symptoms (45.87%). Regardless of the whether an individual experienced difficulty due to current depressive symptoms or not, average PHQ-9 scores identified a mean of 6.892 (SD = 4.811), indicating that the sample demonstrated low depressive symptoms overall. Additionally, CRP was relatively high with a mean of 0.472 mg/dL (SD = 0.737), when compared to the conventional use of a CRP threshold of 3.00 mg/L (0.30 mg/dL) to indicate chronic low-grade inflammation (Osimo et al., 2019). All sample descriptors are listed in Table 1.

When examining associations with difficulty due to current depressive symptoms, we found a number of significant bivariate relationships with both continuous and categorical predictors which can also be reviewed in Table 2. Individuals experiencing difficulty (M = 0.547 mg/dL, SD = 0.861 mg/dL) were found to have higher levels of CRP compared to those not experiencing difficulty (M = 0.410 mg/dL, SD = 0.609 mg/dL), t (917) = −2.82, p < 0.01. This relationship was similar for level of depressive symptoms, with those who were experiencing difficulty (M = 9.253, SD = 5.258) having higher symptomatology than those who did not experiencing difficulty (M = 4.901, SD = 3.269), t (956) = −15.61, p < 0.01. Furthermore, examining the number of close friends revealed that experiencing difficulty (M = 5.594, SD = 4.722) was associated with a lower number of friends than not experiencing difficulty (M = 7.439, SD = 7.654), t (958) = 4.39, p < 0.01. Among sleep related variables, the average number of hours slept per night was significantly lower for those experiencing difficulty due to current depressive symptoms (M = 6.484, SD = 1.736) relative to those not experiencing difficulty (M = 6.821, SD = 1.331), t (962) = 3.40, p < 0.01. Similarly, those experiencing difficulty reported higher rates of not getting enough sleep (M = 2.235, SD = 1.374) relative to those not experiencing difficulty (M = 1.749, SD = 1.276), t (959) = -5.67, p < 0.01. Age also demonstrated mean differences, with experiencing difficulty (M = 54.222, SD = 11.362) being associated with lower age than not experiencing difficulty (M = 57.213, SD = 12.075), t (962) = 3.93, p < 0.01. Lastly, not experiencing difficulty (M = 2.694, SD = 1.660) was associated with lower household income to poverty ratio relative to those that did not experience difficulty (M = 3.031, SD = 1.578), t (884) = 3.09, p < 0.01. Upon inspection of categorical variables, differences were identified between experiencing difficulty and having enough emotional support (χ^2 (1, 32,872,796) = 1,082,175), having a history of a medical condition (χ^2 (1, 32,872,796) = 677,979), having enough financial support (χ^2 (1, 32,872,796) = 406,199), current smoking status (χ^2 (2, 32,872,796) = 681,871), reported vigorous work activity (χ^2 (1, 32,872,796) = 435,559), reported vigorous recreational activity (χ^2 (1, 32,872,796) = 12,561), gender (χ^2 (1, 32,872,796) = 60,574), and racial/ethnic identity (χ^2 (4, 32,872,796) = 93,768). With respect to prescription medication use, differences were also identified between experiencing difficulty and SSRI use (χ^2 (1, 32,872,796) = 197,239), Aspirin use (χ^2 (1, 32,872,796) = 92,297), diuretic use (χ^2 (1, 32,872,796) = 102,944), beta blocker use (χ^2 (1, 32,872,796) = 7783), and ACE inhibitor use (χ^2 (1, 32,872,796) = 16,778).

Correlations were calculated for all continuous predictors using Pearson's r to detect any risk for multicollinearity as well as to help further characterize the relationship between predictors. No risk for multicollinearity was identified among predictor variables as evidenced by no correlations exceeding 0.80. Most notably, CRP was found to have a weak but significant correlation with overall depressive symptoms (r = 0.162, p < 0.01), BMI (r = 0.262, p < 0.01), education level (r = −0.076, p < 0.05), average number of hours slept (r = −0.099, p < 0.01), and how often a participant does not get enough sleep

Table 3
Correlation matrix for continuous variables.

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1-CRP (mg/dL)	1														
2-PHQ9	0.162**	1													
3-Income/poverty	−0.019	−0.224**	1												
4-Education	−0.076*	−0.108**	0.414**	1											
5-Age	0.038	−0.122**	−0.114**	−0.163**	1										
6-BMI	0.262**	0.111**	−0.00009	−0.019	−0.071*	1									
7-Cholesterol (mg/dL)	−0.058	−0.069*	−0.002	0.005	−0.027	−0.085*	1								
8-Systolic	0.045	−0.059	−0.070*	−0.152**	0.440**	0.013	0.072*	1							
9- Diastolic	−0.035	0.046	0.101**	0.050	−0.262**	0.066*	0.183**	0.258**	1						
10-Triglycerides (mg/dL)	0.016	0.008	0.007	−0.030	−0.046	0.201**	0.308**	0.024	0.182**	1					
11-Hours slept	−0.099**	−0.217**	0.065	0.029	0.104**	−0.033	−0.026	0.010	−0.060	−0.032	1				
12- not enough sleep	0.096**	0.310**	0.041	0.044	−0.211**	0.092**	0.064	−0.063	0.115**	0.090**	−0.467**	1			
13-Close friends	0.002	−0.109**	0.118**	−0.010	0.141**	0.050	−0.015	0.004	−0.043	0.014	0.073*	−0.065*	1		
14-Church attendance	0.010	−0.042	−0.093**	−0.078*	0.066*	0.105**	−0.053	−0.043	−0.028	−0.031	0.023	−0.015	0.112**	1	
15-Average alcoholic drinks per day	−0.014	−0.006	0.087**	0.040	−0.277**	−0.097**	0.061	−0.133**	0.117**	0.031	−0.121**	0.058	−0.083**	−0.199**	1

PHQ9: Patient Health Questionnaire 9, CRP: C-reactive protein, BMI: body mass index.
*p < 0.05, **p < 0.01.

($r = 0.096$, $p < 0.01$). Additionally, current level of depressive symptoms were found to correlate significantly with BMI ($r = 0.111$, $p < 0.01$), income to poverty ratio ($r = -0.224$, $p < 0.01$), education level ($r = -0.108$, $p < 0.01$), age ($r = -0.122$, $p < 0.01$), cholesterol ($r = -0.069$, $p < 0.05$), average number of hours slept ($r = -0.217$, $p < 0.01$), how often a participant does not get enough sleep ($r = 0.310$, $p < 0.01$),and number of close friends ($r = -0.109$, $p < 0.01$). Table 3 presents a correlation matrix of all correlations that were calculated for further review.

A multivariate logistic regression analysis was utilized to examine the relationship between CRP and the presence or absence of difficulty due to current depressive symptoms while controlling for several relevant covariates in the areas of biometrics, tobacco and alcohol use, prescription medication use, physical activity, social support, and demographics. Table 4 shows the odds ratio and corresponding 95% confidence intervals for all predictors included in the model. The model shows that CRP has a significant positive relationship with difficulty due to current depressive symptoms. We observed a 13.7% increase (95% CI = 1.135–1.138) in the odds of experiencing difficulty per 1 unit increase in CRP while holding all other variables constant. This significant effect emerged alongside a significant effect for degree of depressive symptoms., with a single point increase in depressive symptoms was associated with a 31.5% increase (95% CI = 1.314–1.315) in the chance of experiencing difficulty due to depressive symptoms while holding all other variables constant. Importantly, where continuous variables were measured, CRP and depressive symptoms both had greater individual magnitude in affecting the odds of experiencing difficulty due to depressive symptoms experienced than did number of church

Table 4
Logistic regression model.

N = 28,149,856	OR	95% CI
PHQ9	1.315	1.314–1.315
Biometric measures		
CRP (mg/dL)	1.137	1.135–1.138
BMI	0.953	0.953–0.953
Triglycerides (mg/dL)	1.000	1.000–1.000
Systolic Blood Pressure	1.001	1.001–1.001
Diastolic Blood Pressure	0.998	0.998–0.998
Cholesterol (mg/dL)	1.001	1.000–1.001
Chronic Condition	2.260	2.255–2.265
Substance use measures		
Current smoking status	0.571	0.569–0.573
History of smoking status	2.018	2.014–2.023
Alcoholic drinks per day	0.906	0.906–0.907
Prescription Medication Use		
SSRI	1.009	1.004–1.013
Aspirin	0.120	0.118–0.121
Diuretic	0.813	0.810–0.816
Beta blocker	1.041	1.037–1.045
ACE inhibitor	1.262	1.252–1.272
Demographics		
Race: Non-Hispanic Black	0.657	0.655–0.659
Race: Mexican American	0.929	0.925–0.933
Race: Other Hispanic	0.322	0.321–0.324
Race: Other	1.418	1.413–1.424
Gender (female = 0)	1.296	1.293–1.298
Age	0.969	0.969–0.969
Family income to poverty ratio	0.995	0.994–0.996
Education	1.102	1.101–1.103
Physical Activity		
Vigorous work activity	0.654	0.653–0.656
Vigorous recreational activity	0.700	0.698–0.702
Social support measures		
Need more support	1.993	1.989–1.997
No financial help	1.301	1.299–1.304
Church attendance per year	0.999	0.999–0.999
Number of close friends	0.962	0.962–0.962

PHQ9: Patient Health Questionnaire 9, CRP: C-reactive protein, BMI: body mass index, SSRI: selective serotonin reuptake inhibitor.
All predictors were significant at the 0.01 level or lower.

attendances (*OR* = 0.999, 95% CI = 0.999–0.999), number of reported friends (*OR* = 0.962, 95% CI = 0.962–0.962), BMI (*OR* = 0.953, 95% CI = 0.953–0.953), triglycerides (*OR* = 1.000, 95% CI = 1.000–1.000), cholesterol (*OR* = 1.001, 95% CI = 1.000–1.001), systolic (OR = 1.001, 95% CI = 1.000–1.001) or diastolic (*OR* = 0.998, 95% CI = 0.998–0.998) blood pressure, average number of alcoholic drinks per day (*OR* = 0.906, 95% CI = 0.906–0.907), age (*OR* = 0.969, 95% CI = 0.969–0.969), education level (*OR* = 1.102, 95% CI = 1.101, 1.103), or family income to poverty ratio (*OR* = 0.995, 95% CI = 0.994–0.996).

In turning to interpretation of the odds ratios for categorical variables in the multivariate model, several additional findings come to light. With respect to social support, perception of needing more emotional support was significantly associated experiencing difficulty due to current depressive symptoms (*OR* = 1.993, 95% CI = 1.989–1.997), whereas perception of not having anyone to turn to for financial assistance was associated with a significantly lower odds of difficulty due to current depressive symptoms (*OR* = 1.301, 95% CI = 1.299–1.304).

Among health-related variables, history of a medical condition (*OR* = 2.260, 95% CI = 2.255–2.265) was associated with an increased risk for experiencing difficulty due to current depressive symptoms, current use of SSRI (*OR* = 1.009, 95% *CI* = 1.004–1.013), beta-blocker (*OR* = 1.041, 95% CI = 1.037–1.045), or ACE inhibitor (*OR* = 1.262, 95% CI = 1.252–1.272). Notably, use of a diuretic (*OR* = 0.813, 95% CI = 0.810–0.816) and aspirin (*OR* = 0.120, 95% CI = 0.118–0.121) were significantly associated with a lower chance of experiencing difficulty due to current depressive symptoms. Similarly, reported engagement in both vigorous work activity (*OR* = 0.654, 95% CI = 0.653–0.656) and vigorous recreational activity (*OR* = 0.700, 95% CI = 0.698–0.702) were also associated with a lower chance of experiencing difficulty due to current depressive symptoms. Additionally, a history of smoking tobacco cigarettes (*OR* = 2.018, 95% CI = 2.014–2.023) was associated with significantly greater odds of experiencing difficulty due to current depressive symptoms, whereas current use of tobacco cigarettes (*OR* = 0.571, 95% CI = 0.569–0.573) is associated with a lower odds of experiencing difficulty due to current depressive symptoms relative to those that reported no use of tobacco cigarettes.

Last, review of demographic categories showed that non-Hispanic Black individuals (*OR* = 0.657, 95% CI = 0.655–0.659), Mexican American individuals (*OR* = 0.929, 95% CI = 0.925–0.933), individuals with an "other" Hispanic identity (*OR* = 0.322, 95% CI = 0.321–0.324) were associated with lower chance of experiencing difficulty due to current depressive symptoms relative to those that identified as non-Hispanic White. However, individuals who identified as an "other" racial/ethnic identity including those of a "mixed" racial ethnic/identity (*OR* = 1.418, 95% CI = 01.413–1.424) were associated with an increased chance of experiencing difficulty due to depressive symptoms relative to those that identified as non-Hispanic White. Finally, men (*OR* = 1.296, 95% CI = 1.252–1.272) showed significantly higher odds for experiencing difficulty due to current depressive symptoms compared to women.

To test the influence of missing data on the overall multivariate model results, two additional models were tested. The first model excluded social support variables, allowing for the inclusion of participants ages 20 and up (n = 49,655,804). This model continued to identify that all included predictor variables were significant but demonstrated an attenuated magnitude for CRP in predicting if participants would experience difficulty due to current depressive symptoms (*OR* = 1.105, 95% CI = 1.104–1.107). The second model excluded the family income to poverty ratio variable due to it having the highest degree of missingness but retained the social support variables. This second model also continued to identify that all predictor variables were significant but showed the greatest magnitude of the three multivariate models in CRP predicting difficulty due to current depressive symptoms (*OR* = 1.192, 95% CI = 1.190–1.193). Complete results for both models can be reviewed in tables five and six in the supplementary materials.

4. Discussion

The present study is the first to demonstrate a significant positive relationship between CRP and difficulty in the psychosocial environment due to the current depressive symptoms, while controlling for the biopsychosocial factors. Although several recent meta-analyses have confirmed a general link between CRP and depression (Osimo et al., 2019; Smith et al., 2018; Horn et al., 2018), and several more studies have confirmed a link between CRP and various aspects of depression, none to our knowledge have demonstrated a linkage between CRP and psychosocial difficulty due to depressive symptoms. Indeed, Wium-Andersen et al. (2013) did identify that CRP was associated with general aspects of psychological distress in individuals with depression or a history of depression; however, here we are able to clarify that psychosocial difficulties can be tied specifically to systemic inflammation as measured by CRP by utilizing a nationally representative sample of older adults (Smith et al., 2018).

The research on the role of CRP in various aspects of depression has seen extensive growth over the last decade. While the aspects of depression that CRP has predicted have remained broad, the consistent theoretical argument is that heightened baseline CRP acts as a proxy for chronic inflammation which may be the true etiological or pathogenic process that is being captured. Many studies have assigned a cut off value for CRP such as >3.0 mg/L or >5.0 mg/L to indicate that these individuals may be experiencing chronic inflammation (Osimo et al., 2019), while some have recommended against inclusion of individuals with CRP values > 10.0 mg/L as this may be a sign of an acute disease process or infection (Sproston and Ashworth, 2018). Because our sample was taken from the general community rather than an inpatient hospital and received a physical from a physician in the process of completing the NHANES survey, we chose to include those with CRP values above 10.00 mg/L (1.00 mg/dL) per the recent recommendations of Moriarity et al. (2021) who found that values of 10.00 mg/L and above may be more strongly associated with depressive illness, although extreme values were winsorized. Consistent with Moriarity et al. (2021) findings, calculation of odds ratios from the present study for CRP values above 10 mg/L indicated a 13.7%–55.6% increased risk for experiencing difficulty due to current depressive symptoms.

A particular strength of the present study was the ability to evaluate the role of both overall depressive symptomatology and CRP on the odds of an individual experiencing difficulty related to current depressive symptoms. Notably, the effect size of depressive symptoms is considerably larger than that of CRP; however, when considered in context of the effect sizes of other predictor variables such as family income to poverty ratio, age, BMI, number of close friends, and number of annual church attendances, CRP has a clear and pronounced effect. One possible explanation for this finding is that CRP may be related more closely to the most impactful symptoms of depressive illness that affect an individual's ability to do their work, take care of things at home, and get along with other people. This is supported by findings that CRP may be related to fatigue (Moriarity et al., 2021), and anhedonia and psychomotor retardation (Felger et al., 2016). Evaluation of CRP as part of a constellation of other factors, such as family history of depression and experience of childhood maltreatment, may show utility in helping guide discussions around referral for psychotherapy or pharmacotherapy so as to be proactive in the prevention or worsening of depression; however, such evaluations methods have yet to be widely implemented (Kraus et al., 2019).

An additional point of novelty in the present study was the control of the influence of perceived social support. Overall, we are able to confirm our initial hypothesis that a higher degree of perceived social support may decrease an individual's likelihood to experience difficulty due to current depressive symptoms; however, review of effect sizes seems to indicate that quality, rather than quantity, of social support may be of greater overall importance for those experiencing depressive symptoms. Calculation of odds ratios for number close of friends based on the sample

mean of 6.595 was associated with a 27.6% decrease in the chance of experiencing difficulty due to current depressive symptoms. Alternatively, identification that one needs greater emotional support was associated with a 99.3% increased chance for experiencing difficulted due to depressive symptoms. This finding seems to fit with the current literature where quality of social support is more strongly associated with past year depression (Werner-Seidler et al., 2017), lower levels of depressive symptoms and hopelessness (Beedie and Kennedy, 2002), and lower levels of stress and depression (Benca-Bachman et al., 2020).

The significance of perceived social support having a negative relationship in the odds of experiencing psychological distress has important implications from an intervention perspective. A component of the current philosophy of treatment for depression is that depressive symptoms should be treated until fully remitted (Keller, 2003; Sobocki et al., 2008). However, many individuals experience depression that is either treatment resistant or has a pattern of chronicity (Spijker et al., 2002). Analyses in the present study may suggest that, while the symptoms of depression do indeed play a role in the likelihood of an individual experiencing psychological distress due to their depression, a focus on building an individual's social support network in their own community may be a strong avenue to decrease the overall burden of depressive illness despite the shortcomings of current treatment methodologies to provide total remission for all those that are affected (Pigott et al., 2010).

The role of social support in inflammation and depression may also provide clues as to why age consistently emerged as having a significant relationship with depression and difficulty due to current depressive symptoms. Indeed, roughly half of the cases of depression in older adults are not new (Fiske et al., 2010), and individuals may have identified stratifies to cope with their depressive symptoms as they age. One being able to distance themselves from past rejection and social pain or learning to forgive the social threats made by others earlier in life, have been hypothesized interventions to reduce depression (Slavich, 2020), and may help explain the association seen across multiple statistical models presented here. However, it is also important to consider that a previous meta-analysis by Mac Giollabhui et al. (2020) found that an association between depression and CRP was largest in older adults, which highlights that findings here that are related to age may be due to qualities of the data such as an age range of 40–80, being cross-sectional, or the sample being comprised entirely of individuals who have endorsed some form of degree symptoms.

In turning to the evaluation of how health related factors may be associated with having difficulty due to depressive symptoms, several notable findings should be highlighted. First, having one of the physical health conditions accounted for by the model is associated with a 126% increased chance for having difficulty due to depressive symptoms, while some form of vigorous activity or current use of Aspirin were each associated with a decreased chance. Indeed, the role of cigarette smoking for those experiencing depression may be equally complex with those who have a history of smoking, but no longer smoke, having an increased risk for difficulty due to depressive symptoms while those who currently smoke have a decreased risk. These findings, in conjunction with previous studies that have identified largely negative outcomes among those who smoke cigarettes while experiencing depression, seem to suggest that the health-related consequences of cigarette smoking may contribute negatively to the experience of depression while the actual act of smoking cigarettes may function as an effective short term coping strategy (Vargas et al., 2013; Nunes et al., 2012).

With respect to demographic predictors, analyses revealed that identity as a racial/ethnic grouping other than non-Hispanic White was associated with a lower chance of experiencing difficulty due to current depressive symptoms for several groups. Racial/ethnic differences in health and health disparities have long been a substantive focus in depression research. Racial disparity frameworks hold that non-Hispanic Black individuals tend to have lower rates of depression than non-Hispanic White individuals; although, this defies conventional wisdom in that 1) non-Hispanic Black individuals tend to have higher exposure to stress which should be associated with higher rates of depression, and 2) non-Hispanic Black individuals tend to have higher rates of physical health problems associated with stress than non-Hispanic White individuals (Mezuk et al., 2013). Debate has emerged on the existence of the paradox, with some holding this as the result of measurement error, employing measures that do not appropriately measure depression in groups other than non-Hispanic White racial/ethnic groupings (Bardwell and Dimsdale, 2001; Mezuk et al., 2013). The present analyses may add an additional layer of findings, suggesting that among individuals who experience depressive symptoms, non-Hispanic White individuals may have a higher chance of experiencing difficulty in the social environment due to of current depressive symptoms; however, this qualification is limited in that difficulty in the psychosocial environment was confined to work, home, and while interacting with other individuals. Indeed, some research suggests that non-Hispanic Black individuals may have heightened biochemical stress indicators such as CRP without experiencing difficulty due to current depressive symptoms depending on aspects of socialization such as alignment with John Henryism (Mezuk et al., 2013; Brody et al., 2013, 2018).

4.1. Limitations

While the present study builds soundly on previous work that examines the relationship between CRP and various aspects of depression, there are several limitations that should be recognized for future groups to improve on. First, our study utilized cross-sectional data. Although we do believe that the analyses presented here demonstrate an important step in understanding how CRP affects various aspects of depressive illness, it is important to acknowledge that the possibility of a bidirectional relationship between experiencing difficulty due to depression and CRP. For instance, individuals who experience difficulty due to depressive symptoms may feel a higher degree of stress than those that do not, possibly leading to higher levels of CRP. Future studies using longitudinal data would strengthen the ability to draw a causal inference. Second, our study utilized a statistical framework focused on the interrogation of main effects of variables. As has been identified in theoretical works (Cohen and Wills, 1985; Uchino et al., 2018a), variables like social support may lend well to interaction models or a structural equation model approach; however, here we have elected to focus on how individual variables might contribute to the chance of experiencing difficulty due to current depressive symptoms in the interest of comparing effect sizes across predictors. Additionally, the inclusion of social support measures reduced the sample by 661 due to original data collection protocols. To assess whether the sample size reduction from inclusion of social support measures influenced our findings, we ran a sensitivity without the social support measures, thus increasing the sample size to 1623 and identified no change in significance. Furthermore, while age demonstrated a negative relationship with both depressive symptoms and difficulty due to depression across several models; the age floor of 40 leaves us unable to fully contextualize the nature that age may play beyond the sample range of ages 40–80. For instance, the relationship between age and depression may be multimodal or U -shaped in samples that are representative on individuals across the whole life course. The analysis showed that there were no differences in statistical significance between the two samples. Last, through the application of the sample weights provided in the NHANES, we may have overpowered our analyses as evidenced by the significance of all predictors in the logistic regression model. We encourage the reader to look to the odds ratios, not necessarily the statistical significance in interpretation of findings.

5. Conclusion

The present study utilized a sample of older adults to explore the relationship between CRP and if an individual will experience difficulty in their social environment due to their depressive symptoms. We incorporated a wide number of relevant covariates that have been known

to be associated with increased CRP levels, depression, or both, and identified that increased CRP levels demonstrated a significant positive relationship with the odds of an individual experiencing difficulty due to their depressive symptoms. Notably, this relationship was significant even while controlling for the effects of depressive symptoms, themselves. Furthermore, the present study incorporated several measures of social support, which may provide additional insights into how community level and personal level supports can be utilized to provide relief for those currently experiencing depression.

Declaration of competing interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2021.100316.

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